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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,932	DEMUTH ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-90* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 7, 10-17, 19, 20, 23-30, 32, 33, 36-43, 45, 46, 49-52, 57 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/09 and 10/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 5,8,9,18,21,22,31,34,35,44,47,48,53-56,58-81 and 83-90.

DETAILED ACTION

1. This action is in response to the reply of June 11, 2009. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn.

Election/Restrictions

2. This application contains newly added claim 90 directed to an invention that is distinct from the elected invention. Claim 90 does not share a corresponding special technical feature with the methods of elected Group I. Claim 90 is drawn to a distinct method for identifying a marker for determining a sensitivity of a lung cancer cell to an agent comprising screening a plurality of genes representing different functional classes, identifying genes from this group that are correlated to a sensitivity to an agent, evaluating an expanded group of genes in the same function class as the identified genes, using expression data to form interactive gene expression indices (IGEIs) and using the IGEIs to develop at least one model that describes an association between expression of a gene and sensitivity of a cancer cell to an agent. These steps are not required for the elected invention of Group I. Further, the elected invention of Group I requires determining if an agent can be used to reduce the proliferation, inhibit the growth or cause the death of a lung cancer cell by assaying for the expression level of ABCC5, GTF2H2 and ERCC2 and identifying an agent as one that can be used to reduce the proliferation, inhibit the growth or cause the death of a lung cancer cell if expression of one of the genes is comparable to that of a gene in cells with known

sensitivity to said agent. These steps are not required to practice the method of new claim 90. Thus, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

3. This application contains claims 5, 8, 9, 18, 21, 22, 31, 34, 35, 44, 47, 48, 53-56, 58-81 and 83-89 drawn to an invention nonelected with traverse in the reply filed on February 29, 2008 and July 12, 2007, and newly added claim 90. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1-90 are pending.

Claims 5, 8, 9, 18, 21, 22, 31, 34, 35, 44, 47, 48, 53-56, 58-81 and 83-90 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-4, 6, 7, 10-17, 19, 20, 23-30, 32, 33, 36-43, 45, 46, 49-52, 57 and 82 have been examined herein to the extent that the claims read on the elected invention which requires determining the level of expression of the combination of ABCC5, GTF2H2 and ERCC2 by assaying for the level of said nucleic acids. The subject matter of assaying for protein levels (invention II) is withdrawn from consideration as being drawn to a non-elected invention.

Claim Objections

5. Claims 1, 7, 10-14, 20, 23-27, 33, 36-40, 46, 49-52, 57 and 82 are objected to because the claim includes subject matter of the non-elected inventions, namely the determination of the level of protein by detecting proteins.

Response to Remarks:

In the reply of June 11, 2009, Applicants state that the claims have been amended so that they are limited to the elected invention of detecting the expression level of ABCC5, GTF2H2 and ERCC2. Applicants request that the objection be withdrawn in view of the amendment to the claims.

This argument and the amendment to the claims have been thoroughly considered but are not sufficient to obviate the objection. The claims as amended still encompass methods which assay for the level of ABCC5, GTF2H2 and ERCC2 proteins (invention II), whereas the elected invention is limited to methods which assay for the level of ABCC5, GTF2H2 and ERCC2 nucleic acids (invention I). Accordingly, it is maintained that the claims still encompass the subject matter of non-elected invention II.

6. Claim 82 is objected to because of the following informalities:

Claim 82 recites "the levels of expression marker genes" whereas it appears that the claim should recite "the levels of expression <u>of</u> marker genes."

Appropriate correction is required.

Maintained Rejections

Claim Rejections - 35 USC § 112 second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 20, 33, 46 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 20, 33 and 46 are indefinite over the recitation of IGEI. The specification does not provide a clear definition for this term, the claims do not define this term and there is no art recognized definition for this term. The specification (page 50) provides an example of an IGEI, stating that "(t)hese data were combined into interactive gene expression indices (IGEI) by placing one ore more genes directly associated with the phenotype in the numerator and one or more genes negatively associated with the genotype in the denominator using the quantitative reverse transcriptase-PCR method described in Willey." However, this example is not considered to constitute a limiting definition for the term "IGEI." Further, while the claims have been amended to indicate that an IGEI comprises a ratio of expression of at least two marker genes, it is unclear as to the relationship between the undefined "at least two marker genes" and the marker genes of ABCC5, GTF2H2 and ERCC2. It is also unclear as to how the ratio would be considered when the "at least two markers" comprise 3 or 4 or 5 markers. For instance, if the ratio would be that of marker 1 over marker 2, or the ratio of marker 1 over marker 2 plus marker 3, or the ratio of marker 1 over marker 2 minus marker 3. In the absence of a clear definition for this phrase, one of skill in the art cannot determine the meets and bounds of the claimed invention.

Response to remarks:

In the response, Applicants traverse this rejection by stating that the rejection has been obviated by the amendment to recite that the ICEI comprises the ratio of the level of expression of at least two marker genes. However, the claims describe the IGEI in terms of two different properties - one in which the level of expression of ABCC5,

GTF2H2 and/or ERCC2 are “used” to form the IGEI and one in which the IGEI comprises the ratio of any two marker genes. It is unclear as to the relationship between the two differently defined IGEIs and the relationship between the marker genes of ABCC5, GTF2H2 and ERCC2 and the other "at least two marker genes."

New grounds of rejection necessitated by Applicant’s amendments to the claims:

Claim 57 is indefinite over the recitations of “said agent-exposed cancer cells” because this phrase lacks proper antecedent basis. While the claim previously refers to “non small cell lung cancer cells” that are exposed to an agent, the claims do not previously refer to “agent-exposed cancer cells.”

Claim Rejections - 35 USC § 112 - Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 7, 10-17, 19, 20, 23-30, 32, 33, 36-43, 45, 46, 49-52, 57 and 82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection was previously presented in the Office action of October 10, 2008 and is maintained for the reasons set forth therein.

Response to Remarks:

In the response, Applicants traversed this rejection.

Applicants state that the rejection as it pertains to the lack of enablement for methods which assay for the expression of siRNAs and miRNAs has been obviated by the amendment to claims 3, 16, 29 and 42 to delete the reference to siRNAs and miRNAs. However, claims 3, 16, 29 and 42 depended from claims 2, 15, 28 and 41 which recites assaying fro a transcribed polynucleotide. As defined in the specification, and as evidenced by the claims as originally filed, transcribed polynucleotides encompass siRNAs and miRNAs. Accordingly, the claims as broadly written still encompass the detection of siRNAs and miRNAs of ABCC5, GTF2H2 and ERCC2. However, the specification has not enabled the use of such siRNAs and miRNAs for the reasons set forth in the Office action of October 10, 2008.

Regarding the enablement rejection as it pertained to any type of cancer cell, Applicants assert that the rejection has been obviated by the amendment to the claims to recite that the expression level is determined in lung cancer cells. However, all information provided in the specification regarding the expression level of ABCC5, ERCC2 and GTF2H2 is limited to non-small cell lung cancer (NSCLC) cell lines. The response does not provide any arguments or evidence to explain why the results obtained with NSCLC cell lines can be extrapolated to any primary lung cancer cell or any lung cancer cell line.

Applicants traverse the rejection by stating that the methods for identifying agents effective to treat lung cancer do not require that the markers are related to or correlated with the occurrence of cancer. It is asserted that the specification teaches that the level of expression of ABCC5, GTF2H2 and ERCC2 is correlated with agents

for treating cancer. However, this characterization of the specification is not accurate. In fact, the specification teaches that expression levels of GTF2H2 alone were **not** correlated with response of NSCLC cells to cisplatin treatment (see Table 3). Note that each of the present claims requires determining the level of GTF2H2 polynucleotides in order to identify an agent that reduces cancer cell proliferation, inhibits cancer cell proliferation, causes cancer cell death or modulates onset or progression of cancer. The response does not address why the specification is enabling for using GTF2H2 expression levels to identify agents that reduce the proliferation of, inhibit the growth of or cause the death of lung cancer cells. The response does not point to any teachings in the specification which provide guidance for how to use gene expression of GTF2H2 to identify agents to treat cancer cells and does not explain why or how a gene whose expression level is not correlated with response to cisplatin treatment can be used to identify cisplatin or similar platin agents that are effective for reducing proliferation, inhibiting growth or causing the death of lung cancer cells.

Further, the results in the specification are limited to only NSCLC cell lines treated with cisplatin, whereas the present claims are inclusive of methods which analyze expression levels in response to any type of agent in any primary lung cell or cell line. That is, Table 3 indicates that ABCC5 and ERCC2 mRNA levels were correlated with chemoresistance of NSCLC cell lines to cisplatin. In Table 4 (Figure 4), it is reported that the ratios of ERCC2/GTF2H2 and ABCC5/GTF2H2 were correlated with response to cisplatin in NSCLC cell lines, with R^2 values of 0.90 and 0.91, and p values of 0.0004 and 0.0002, respectively. However, the present claims are not limited to

methods which assay NSCLC cell lines for the level of ABCC5 mRNA, ERCC2 mRNA, the ratio of ERCC2/GTF2H2 mRNA, or the ratio of ABCC5/GTF2H2 mRNA to predict the responsiveness of the NSCLC cell line to cisplatin.

Applicants state that the claims as amended are drawn to methods comprising comparing gene expression in lung cancer cells with previously determined levels in cells with known sensitivity to agents to determine the sensitivity of cells to a drug. However, it remains unclear as to how this amendment results in the enablement of the claims. If a cell line is known to be sensitive to an agent such as carboplatin and has a particular expression level of ABCC5, ERCC2 and/or GTF2H2, then how does the same level of expression of ABCC5, ERCC2 or GTF2H2 mRNA in that cell or a different cell indicate that an agent can be used to treat cancer? If there is no relationship between expression levels of ABCC5, ERCC2 or GTF2H2 and lung cancer, it remains unclear as to why one would conclude that a cell that is sensitive to an agent or is not sensitive to an agent has this property due the levels of ABCC5, ERCC2 or GTF2H2 mRNA. Given the vast multitude of other mRNAs expressed in lung cancer cells, one cannot predictably determine which of the mRNAs are correlated with a cell's property of being sensitive to a drug or a cell's property of not being sensitive to a drug. Clearly, knowledge that a cell has some level of sensitivity or non-sensitivity to an agent would not lead one to the conclusion that the ABCC5, ERCC2 or GTF2H2 mRNA levels in that cell are the cause of that sensitivity or lack of sensitivity in the absence of any relationship between the ABCC5, ERCC2, and GTF2H2 mRNA levels and cancer or responsiveness of a lung cancer cell to an agent.

It is also noted that the claims include comparing the mRNA levels to those in cells with "known sensitivity to an agent." Such cells thereby include cells that are either sensitive or non-sensitive to an agent. Thus, the claims indicate that if a mRNA level is the same in a test cell treated with an agent as compared to a cell that is known to not be sensitive to an agent, one would conclude that the agent can be used to reduce the proliferation, inhibit the growth or cause the death of a lung cancer cell. However, it is unclear as to how the mRNA levels can be the same in both a cell sensitive to an agent and a cell not sensitive to an agent and that regardless of whether the cell is sensitive or not sensitive to an agent, the presence of a comparable level of expression would indicate that the agent can be used to reduce the proliferation, inhibit the growth or cause the death of a lung cancer cell.

The response further asserts that the specification teaches methods for determining gene expression levels and methods for using IGEIs to predict phenotypes. The response states that "The references cited by tile Examiner to illustrate tile unpredictability further exemplifies the innovation of the instantly claimed invention as the references do not generate a model of IGEI values and selecting validated IGEI values for use in predicting and monitoring cancer treatments."

This argument has been fully considered but is not persuasive. The present claims are not drawn to general methods for assaying for assaying for the level of expression of ABCC5, ERCC2 and/or GTF2H2. The examiner agrees that such general methods of assaying for ABCC5, ERCC2 and/or GTF2H2 mRNA levels are well known in the art. If the claims were directed to such methods, such methods would be

rendered anticipated or obvious over the prior. However, the present claims require more than determining ABCC5, ERCC2 and GTF2H2 mRNA levels. The claims require identifying agents that can be used to reduce the proliferation, inhibit the growth or cause the death of a lung cancer cell based on whether the level of ABCC5, ERCC2 and/or GTF2H2 mRNA is the same or different in the cell analyzed as compared to a cell that is either sensitive to an agent or is not sensitive to an agent. Thus, the unpredictability in the art is not based on whether one would know how to assay for mRNA levels but rather on the unpredictability of determining an association between ABCC5, ERCC2 and GTF2H2 mRNA levels and the responsiveness of lung cancer cells to agents that reduce the proliferation, inhibit the growth or cause the death of a lung cancer cell. It is unclear as to how Applicants draw the conclusion that the cited references exemplify the innovation of the claimed methods. In fact, the cited references establish that the claimed mRNAs do not show any alteration in expression in response to treatment of particular cancer cells to particular agents. For example, Young teaches that ABCC5/MRP5 mRNA levels varied between SCLC and NSCLC cell lines (page 677, col. 1). This suggests that there is no absolute level of ABCC5/MRP5 mRNA present in all lung cancer cell types and that the results obtained with one cell type (either sensitive or non-sensitive to an agent) cannot be extrapolated to other lung cancer cell types. Similarly, Kool analyzed ABCC5/MRP5 mRNA levels in human cancer cell lines sensitive or resistant to treatment with doxorubicin or cisplatin. Kool reported that ABCC5/MRP5 mRNA levels varied significantly between different types of human tissues (Table 2). Kool concluded that while ABCC5/MRP5 is overexpressed in

some resistant cell lines, there is no clear correlation between ABCC5/MRP5 mRNA levels and resistance to doxorubicin or cisplatin (see abstract and page 3538, col. 1). Since the findings obtained with one resistant cell line cannot be extrapolated to other resistant cell lines, it would be similarly unpredictable as to whether mRNA levels in a test cell can be predictably compared to mRNA levels in any one cell line known to be resistant to an agent. Additionally, Oguri was cited for its teachings of detecting ABCC5/MRP5 mRNA expression in both normal lung and lung cancer cells in vivo following exposure to carboplatin (page 99). mRNA levels of ABCC5/MRP5 were significantly higher in tissues from patients who had been previously exposed to platinum drugs in vivo than from patients who had not been previously exposed to platinum drugs (page 98, col. 2). The authors also report that ABCC5/MRP5 mRNA levels were not rapidly induced by platinum drugs either in lung cancer cell lines or in PMN cells within 24 hours (see abstract). The teachings of Oguri highlight the unpredictability in the art and the variety of factors which must be considered when interpreting results of screening assays, including time of exposure to an agent, use of cells previously exposed to an agent as compared to cells not previously exposed to an agent, and the relevance of comparing gene expression levels normal cells and cancer cells. The response does not address why such factors would impact the claimed methods in which the mRNA levels in a test cell treated with an agent are compared with any other type of cell with a known sensitivity to an agent.

Lastly, it is noted that claims 40-43, 45, and 49-52 are directed to methods wherein a new cancer treatment is identified comprising determining the level of

ABCC5, ERCC2 and GTF2H2 mRNA in a lung cancer cell exposed to the potential cancer treatment and the treatment is considered to be effective for treating cancer if the level of one of the mRNAs is comparable to that of the level of mRNA in any type of cell with a known sensitivity to "a cancer agent." The response does not address the unpredictability of extrapolating the results obtained with one cancer treatment agent to other cancer treatment agents. Given that the response asserts that there need not be any correlation between the mRNA levels and the occurrence of cancer, it remains unclear as to how one can extrapolate the findings obtained in a lung cancer cell treated with an unknown agent to any other type of cell treated with any other agent. Applicants do not provide any evidence or cogent arguments to support such a conclusion.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634